Contact and encirclement of glioma cells in vitro is an intrinsic behavior of a clonal human neural stem cell line.

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Public Summary:
Glioblastoma multiforme (GBM) is essentially untreatable because portions of the tumor invading normal brain are inaccessible to conventional therapies. Neural stem cells (NSCs) are intrinsically attracted to tumor sites in the brain, and have the potential to act as vehicles to deliver therapeutic agents to these otherwise inaccessible cancer cells. In glioma, NSCs are found in close contact with tumor cells, raising the possibility that NSC may preferentially form contacts with glioma tumor cells and not other types of cells. To better understand the mechanisms underlying NSC interactions with glioma cells, we examined NSC-target cell contacts in a highly simplified 3-dimensional peptide hydrogel (Puramatrix) in which cell behaviors can be studied in the relative absence of external cues. HB1.F3 is an immortalized clonal human NSC line extensively characterized in preclinical investigations. Using high-resolution confocal microscopy, NSCs were observed contacting or encircling glioma cells, but never the reverse. Next, examining specificity of these contacts, no significant differences in either percentages of NSCs contacting targets, or in the extent of target cell encirclement, were observed when NSCs were presented with various potential target cells (human glioma and breast cancer cell lines, patient-derived brain tumor lines, non-tumor fibroblasts, primary mouse and human astroglial cells, and primary adult and newborn human dermal fibroblasts) except that interactions between NSCs cells did not progress beyond establishing contacts. We conclude that formation of contacts and subsequent encirclement of target cells by NSCs is an intrinsic property, and that preferential contact formation with tumor cells in vivo must therefore be highly dependent on the microenvironment and cues originating in the and interface between tumor and brain.

Scientific Abstract:
Pathotropic neural stem and/or progenitor cells (NSCs) can potentially deliver therapeutic agents to otherwise inaccessible cancers. In glioma, NSCs are found in close contact with tumor cells, raising the possibility that specificity of NSC contact with glioma targets originates in the tumor cells themselves. Alternatively, target preferences may originate, at least in part, in the tumor microenvironment. To better understand mechanisms underlying NSC interactions with glioma cells, we examined NSC-target cell contacts in a highly simplified 3-dimensional peptide hydrogel (Puramatrix) in which cell behaviors can be studied in the relative absence of external cues. HB1.F3 is an immortalized clonal human NSC line extensively characterized in preclinical investigations. To study contact formation between HB1.F3 NSCs and glioma cells, we first examined co-cultures of eGFP-expressing HB1.F3 (HB1.F3.eGFP) NSCs and dsRed-expressing U251 glioma (U251.dsRed) cells. Using confocal microscopy, HB1.F3.eGFP cells were observed contacting or encircling U251.dsRed glioma cells, but never the reverse. Next, examining specificity of these contacts, no significant quantitative differences in either percentages of HB1.F3 NSCs contacting targets, or in the extent of target cell encirclement, were observed when HB1.F3.eGFP cells were presented with various potential target cells (human glioma and breast cancer cell lines, patient-derived brain tumor lines, non-tumor fibroblasts, primary mouse and human astroglial cells, and primary adult and newborn human dermal fibroblasts) except that interactions between HB1.F3 cells did not progress beyond establishing contacts. Finally cytoskeletal mechanisms employed by HB1.F3.eGFP cells varied with the substrate. When migrating in Puramatrix, HB1.F3 NSCs exhibited intermittent process extension followed by soma translocation, while during encirclement their movements were more amoeboid. We conclude that formation of contacts and subsequent encirclement of target cells by HB1.F3 NSCs is an intrinsic property of these NSCs, and that preferential contact formation with tumor cells in vivo must therefore be highly dependent on microenvironmental cues.